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Rational Catalysis Design on the Basis of Mechanistic Understanding: Highly Efficient Pd-Catalyzed Cyanation of Aryl Bromides with NaCN in Recyclable Solvents

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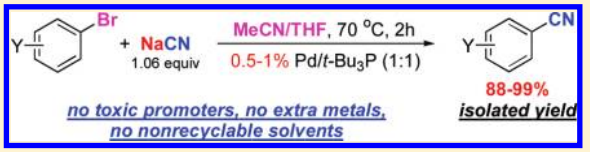
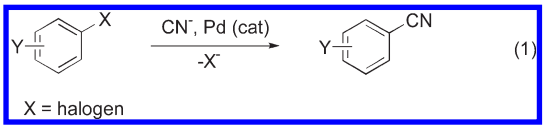
Supporting Information

ABSTRACT: Rational catalysis design on the basis of a detailed mechanistic understanding has been used to successfully develop the first efficient general Pd-catalyzed aromatic cyanation reaction under the highly sought after practicable conditions: (i) MCN (M = Na or K) as a cyanide source; (ii) low-boiling recyclable solvents; and (iii) minimal quantities of inexpensive, nontoxic promoters. The developed catalytic reaction converts aromatic bromides to the corresponding nitriles in 88−99% isolated yield with NaCN and 0.5−1.0 mol % of a *t*-Bu_3P-monoligated Pd catalyst in MeCN-THF within 2 h at 70 °C. The process exhibits high functional group tolerance.



INTRODUCTION

Aromatic nitriles constitute an important class of compounds that are widely used as building blocks and intermediates for the synthesis of pharmaceuticals, agrochemicals, dyes, and specialty materials.[1] One of the most attractive modern methods to selectively introduce a cyano group into the aromatic ring is Pd-catalyzed cyanation of haloarenes (eq 1) first reported by Takagi et al. as early as 1973.[2,3]



(1)

Looking deceivingly simple, reaction 1 is conceivably the least reproducible and most unpredictable of all Pd-catalyzed transformations of aromatic halides. The notoriously facile deactivation of the Pd catalyst by excess cyanide has been widely recognized since the original work by Takagi's group[4,5] in the 1970s, and more recently studied in detail both empirically[6] and mechanistically.[7] Ironically, the most industrially attractive sources of cyanide, ionic NaCN and KCN, are particularly poisonous to the catalyst. To obviate the problem of quick catalyst deactivation, several efficient techniques have been developed, including use of dipolar aprotic solvents (DMF, NMP, HMPA, DMAC, etc.) at elevated temperatures and of cyanide sources that are better tolerated by the catalyst, such as $Zn(CN)_2$, $K_4[Fe(CN)_6]$, Me_3SiCN, and acetone cyanohydrin.[1] Particularly widely used are $Zn(CN)_2$ and $K_4[Fe(CN)_6]$, originally introduced for the purpose by a group of Merck scientists[8] and Beller et al.,[9] respectively. While representing excellent sources of cyanide for reaction 1, both $Zn(CN)_2$ and $K_4[Fe(CN)_6]$ are not ideal for larger scale operations,[1f] especially in aprotic dipolar solvents. Not only are such nonrecyclable solvents costly, but also potential contamination of certain industrial products and/or intermediates with even small quantities of Zn and Fe is undesired. The well-performing $Zn(CN)_2$/DMF system also creates significant problems in the isolation step upon its dilution with large quantities of water (up to >10-fold), followed by product extraction. After the challenging filtration of the resultant multiphase liquid−solid system to separate large quantities of finely dispersed zinc inorganics, the DMF cannot be recovered from the large volumes of the aqueous phase. The latter is therefore incinerated at a considerable extra cost and certainly not to the benefit of the environment.

The development of Pd-catalyzed aromatic cyanation with NaCN or KCN in recyclable solvents for genuinely practicable processes has been highly sought after.[10] Little progress, however, has been made toward this important goal. In 1975, Sekiya and Ishikawa[11] reported the formation of benzonitrile in 82% yield from iodobenzene, KCN (1.5 equiv), and $[(Ph_3P)_4Pd]$ in THF under reflux for 8 h. The Pd catalyst loading was high (20 mol %) and no other haloarene substrates were explored. Later on, Anderson and co-workers[12] found this protocol ineffective for other iodoarenes, rightly noting that "the $Pd(PPh_3)_4$-mediated process is recognized as being notoriously unreliable". In full accord with this, Takagi[13] has reported only 32% yield of PhCN from PhI in THF in the presence of a much more active Pd-dppf catalyst, whereas in NMP, the formation of benzonitrile under similar conditions was nearly quantitative. To make the process viable, various additives have been used, including large quantities of alumina,[14] Cu or Zn salts (10−50 mol %),[12,15] organotin compounds,[16] as well as nitrogen co-ligands/bases such as tetramethylethylenediamine (TMEDA) and 1,1-methylenedipiperidine (20 mol %).[17] In the latter case, the cyanation with KCN was performed at high temperatures (140−160 °C) in

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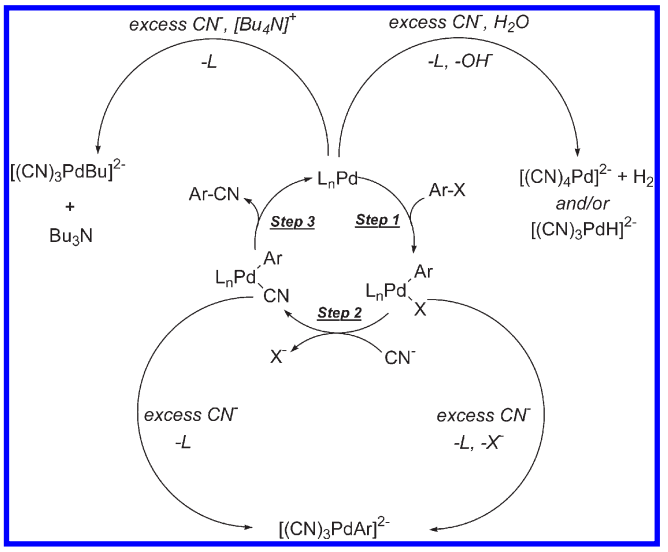
Scheme 1



toluene or mesitylene. The reactions in toluene (bp = 110−111 °C) had to be carried out in sealed reactors under pressure. Obviously, the additives, especially if they are toxic (Sn) and/or must be used in large amounts, severe reaction conditions, and the necessity to run the process employing hazardous cyanide under pressure have a negative impact on both the practical value and safety of the method.

Nearly 40 years after the original discovery,[2] an efficient and safe Pd-catalyzed aromatic cyanation reaction that employs MCN (M = Na or K) in a recyclable solvent in the absence of undesirable additives in large quantities still remains a challenge that has not yet been met. Herein, we report the first example of a general process like this for the synthesis of aromatic nitriles from the corresponding bromides in nearly quantitative yield. This process employs 0.5−1.0 mol % Pd and minimal quantities of inexpensive, nontoxic promoters.

RESULTS AND DISCUSSION

Unlike previous empirical developments in the area, this work is based on detailed mechanistic information. We used our recently acquired understanding[7,18] of Pd catalyst deactivation pathways in reaction 1 (Scheme 1) as the foundation for a rational design of the desired catalytic process. The following considerations have been used as guidelines.

1. The reaction should be carried out under anhydrous, proton source-free conditions in order to avoid the formation of HCN via hydrolysis of the cyanide anion. As one of us has demonstrated earlier,[7] HCN is much more reactive toward Pd(0) than any haloarene substrate (Scheme 1, Step 1). The reaction of HCN with zerovalent palladium leads quickly and irreversibly to $[Pd(CN)_4]^{2-}$ and/or $[(CN)_3Pd(H)]^{2-}$ that are catalytically inactive.
2. Cyanide concentration in the liquid phase of the reaction mixture should be comparable to that of the Pd catalyst. Low $[CN^-]$ would starve the catalyst for cyanide, resulting in slower reaction rates and possibly side-processes at the metal center. On the other hand, for $[CN^-] \gg [Pd]$, quick catalyst deactivation would occur via irreversible displacement of the stabilizing phosphine ligands (L) on Pd by cyanide in Steps 2 and 3 of Scheme 1.[7,18] Among recyclable aprotic solvents, MeCN and THF were selected as suitable candidates because both dissolve NaCN and KCN, the reported[19] solubilities of ca. 2−10 mmol L^{-1} at 60 °C being commensurate with the projected Pd catalyst concentration. Chlorinated and hydrocarbon solvents were rejected because they do not dissolve NaCN and KCN. In addition, chlorinated solvents can be reactive toward electron-rich Pd(0) intermediates involved in the catalytic cycle. The desired concentration of CN^- from an alkali metal cyanide in aromatic solvents such as toluene could be achieved by using a phase-transfer agent. However, the most attractive and readily available phase-transfer catalysts, quaternary ammonium salts, should be avoided because they react with mixed cyano phosphine Pd(0) anionic species, rendering the catalyst inactive (Scheme 1).[7] Other types of phase-transfer agents such as crown ethers might be suitable, yet are much less attractive cost-wise.
3. The stabilizing tertiary phosphine ligand should bind tightly to Pd to impede its displacement by cyanide when the metal is in the oxidation state +2 (Scheme 1, Steps 2 and 3). On the other hand, tricoordinate Pd intermediates should be easily accessible to lower activation barriers to the transformations involved in the catalytic cycle, especially the product forming reductive elimination step.[20] It was reasoned that *t*-Bu_3P[21] should meet both requirements, so long as it is used in the amount of 1 equiv per Pd.[22] Furthermore, *t*-Bu_3P has proven efficiency in Pd-catalyzed cyanation of haloarenes with $Zn(CN)_2$ in DMF[23,24] or with KCN in the presence of an organotin promoter.[16]
4. No matter what precautions are taken, the catalyst still undergoes deactivation under real-life conditions: (i) commercially alkali metal cyanides always contain small quantities of water and (ii) phosphine displacement by cyanide is hardly possible to avoid altogether. The polycyano Pd(II) products of the catalyst poisoning processes (Scheme 1) are extremely robust and unreactive due to the exceptionally strong affinity of divalent palladium for cyanide. The catalytic activity may be regained via reduction of the Pd(II) to Pd(0) whose binding to cyanide is not nearly as strong.[7] That is why running reaction 1 in the presence of small quantities of a carefully selected reducing agent usually can have a tremendous beneficial effect on the process. Apart from metal powders (usually Zn dust) traditionally used for that purpose,[1] polymethylhydrosiloxane[25] and isopropyl alcohol[26] have recently been employed. In our studies, we leaned toward use of inexpensive inorganic reductants, including Zn dust.

The above considerations served as the starting point for the study involving bromobenzene as a model compound. Careful optimization of the process was undertaken, as summarized in Table 1.

Cyanide Source. Of the two ionic cyanide sources, NaCN and KCN, the sodium salt was chosen because of its lower cost and higher solubility in THF and MeCN.[19] A minimal excess (6%) of NaCN (97% purity) was employed to ensure full conversion. The salt was finely ground for efficient mass transfer.

Catalyst. The catalyst was prepared by premixing a Pd(0) dba complex with *t*-Bu_3P. Easier to handle $[t\text{-}Bu_3PH]^+$ salts[27] are a proton source and hence were not used to avoid the formation of HCN that strongly deactivates the catalyst (see above). Although acetonitrile was found to be a better solvent for the reaction

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Table 1. Optimization of Pd-Catalyzed Cyanation of Bromobenzene

entry	Pd, %	additive, mol %	MeCN volume, mL	time, h	conversion, %
1	1	-	4	2	91
2	1	Zn, 8%	4	2	100
3	1	Zn, 4%	4	2	100
4	0.65	Zn, 4%	4	1	60
5	0.35	Zn, 4%	4	2	40
6	0.5	Zn, 4%	2	1	31
7	0.5	Zn, 4%	4	2	40
8	0.5	Zn, 4%	8	1	47
9	0.5	Zn, 4%	10	1	43
10	0.5	Zn, 4%; 1 mL Hex	4	1	40
11	0.5	Zn, 4%; NaO(*t*-Bu), 3%	4	1	2
12	0.5	Zn, 4%; KOH, 1%	4	1	1
13	0.5	Zn, 4%; KOH, 2,5%	4	1	1
14	0.5	Zn, 4%; KOH, 5%	4	1	1
15	0.5	Zn, 4%; NaH, 5%	4	1	25
16	0.5	Zn, 4%; CaH_2, 3%	4	1	49
17	0.5	Zn, 4%; CaH_2, 6%	4	1.5	75
18	0.5	Zn, 4%; CaH_2, 12%	4	1.5	74
19	0.5	CaH_2, 6%	4	1	67
20	0.5	TMEDA, 2%	4	1	0
21	0.5	TMEDA, 5%	4	1	0
22	0.5	DMF, 10%	4	2	75
23	0.5	CaH_2, 6%; DMF, 10%	4	1	93
24	0.7	CaH_2, 6%; DMF, 5%	4	1	99
25	0.7	Zn, 4%; DMF, 5%	4	1	99
26	0.7	CaH_2, 6%; acetone, 5%	4	1	99
27	0.7	Zn, 4%; acetone, 5%	4	1	99

(see below), the catalyst was generated in THF because of the poor solubility of the Pd(0) source in MeCN. To ensure the highest catalytic activity, the Pd to *t*-Bu_3P molar ratio was maintained at 1.[28] In this work as well as in our previous studies employing dba Pd(0) complexes, it was noticed that the classical Ishii method[29] for making $Pd_2(dba)_3$ from $PdCl_2$, dba, and NaOAc in MeOH affords, in nearly quantitative yield, a composition that consistently analyzes, without recrystallization, as $Pd_2(dba)_5$ rather than $Pd_2(dba)_3$ or $Pd(dba)_2$.[30] No "extra" dba could be removed from this material that likely consists of $Pd_2(dba)_3$, $Pd(dba)_2$, and $Pd(dba)_3$.[31−34] Therefore, the empirical composition $Pd_2(dba)_5$, as established by elemental analysis, was used for calculations to achieve the desired Pd to *t*-Bu_3P molar ratio of 1.

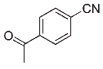
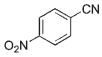
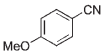
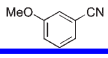
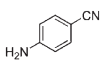
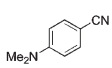
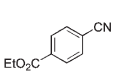
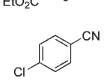
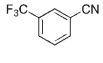
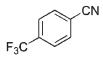
Solvents. In the initial series of experiments, it was found that the reaction in MeCN was faster and more reproducible than in THF. As the catalyst was used as a THF solution (see above), in most of the optimization experiments (Table 1) the solvent consisted of 4 mL of MeCN and 0.35−1 mL of THF at [Pd] ≈ 2.6−8.0 mmol L^{-1}. This range was used to roughly match the reported[19] solubility of NaCN in MeCN = 4.4 mmol L^{-1} at 60 °C and thereby ensure that the liquid phase would not contain cyanide in large excess to poison the catalyst.[35]

Reducing Agents and Additives. Initially, Zn dust was used as a reducing agent. It is conceivable that the small quantities of Zn salts formed upon reactivation of the poisoned catalyst (see above) might also promote the reaction.[36] Later it was found, however, that finely ground CaH_2 is also a good promoter for the reaction, especially if used in the presence of small quantities of DMF or acetone (5%). Under the reaction conditions, the role of CaH_2 might also include sequestering adventitious HCN that deactivates the catalyst.[7] Other bases were also tested.

For optimization, the reaction of bromobenzene with NaCN (1.06 equiv) was first carried out with 1 mol % of the catalyst without any additives to reach 91% conversion to PhCN at >99.9% selectivity (GC−MS) after 2 h at 70 °C (Table 1, entry 1). Repeating the run in the presence of Zn dust (8 or 4 mol %) raised the conversion to 100% without any loss in selectivity (Table 1, entries 2 and 3). However, when the amount of the catalyst was reduced to 0.65% and further to 0.35%, the conversion dropped to 60 and 40%, respectively. A number of additives were then screened to achieve quantitative yield of PhCN with 0.5% Pd (entries 6−23). Varying the Pd to CN^- ratio by changing the volume of the reaction mixture (entries 6−9) and by adding hexane (entry 10) did not lead to improvements.

Strong bases, KOH and *t*-BuONa (1−5%), were found to deactivate the catalyst (entries 11−14), and an inferior conversion of only 25% was obtained upon addition of NaH (entry 15). TMEDA (2−5%) also destroyed the catalytic activity (entries 20 and 21), in contrast to the reported[17] beneficial effect of this diamine on the high-temperature aromatic cyanation of chloroarenes. Importantly, CaH_2 was found to promote the reaction (entry 19), especially if used in conjunction with DMF. Thus, remarkably high conversion of 93% was observed with only 0.5% Pd in the presence of CaH_2 (6%) and DMF (10%). The yield of 93% was the highest ever achieved in this study with 0.5% Pd catalyst (entry 23).

Table 2. Pd-Catalyzed Cyanation of Bromoarenes[a]

Entry	Substrate	Pd, %	Time, h	Product	Conversion, % CaH_2 (Method A)	Conversion, % Zn (Method B)	Isolated yield, % (Method)
1		0.7	2		100	100	>99[b]
2		0.7	2		100	100	99(B)
3		0.7	2		96	98	93(B)
4		0.7	2		98	84	97(A)
5		0.7	2		99	100	94(B)
6		0.7	2		100	-	99(A)
7		0.5	2		100	100	99(B)
8		0.5	2		100	100	99(B)
9		1	2		75	100	99(B)
10		0.7	2		98	99	99(B)
11		1	2		100	100	99(B)
12		0.7	2		100	100	99(B)
13		0.7	2		100	100	99(B)
14		0.7	2		100	100	99(B)
15		0.7	2		98	97	95(B)[c,d]
16		1	2		100	100	97(B)[c]
17		1	2		100	100	93(B)
18		0.7	2			100	88(B)
19		0.7	1[e]		30	75	NI[f]
20		0.7	4[e]			42	NI[f]

[a] For reaction conditions and specifics, see the Experimental Section. [b] GC−MS yield. [c] NMR yield. [d] Small quantities (3−5%) of phthalodinitrile were co-produced as a result of C−Cl bond cyanation. [e] No change in conversion after longer time. [f] NI = not isolated.

To reach conversions exceeding 93%, the amount of the catalyst was increased to 0.7 mol %. That indeed resulted in quantitative yield of PhCN (entries 24 and 25), consistently observed in a number of repeats employing Zn dust (4%) or CaH_2 (6%) in the presence of DMF (5%). In search of a less costly and more easily removable alternative to DMF, it was found that it can be successfully replaced with an equal amount (5%) of acetone (entries 26 and 27). The optimized conditions were then used to cyanate other substrates.

Cyanation of Substituted Aryl Bromides. Under the optimized conditions, a number of bromoarenes were successfully converted to the corresponding nitriles, mostly in quantitative yield (Table 2). The reaction smoothly proceeds with substrates bearing electron-donating and electron-withdrawing substituents, exhibiting virtually 100% selectivity and excellent functional group tolerance. Even 4-dimethylaminobromobenzene and bromoanilines could be cyanated in quantitative yield (Table 2, entries 11−13). In most cases, 0.7 mol % of the Pd catalyst was used, although with more reactive electron-deficient substrates quantitative conversions were obtained with even less Pd (0.5%; entries 7 and 8). For some of the less reactive aryl bromides (entries 9, 11, 16, and 17), a slightly higher catalyst loading was used (1%) to achieve full conversion. Each reaction was successfully reproduced at least three times. All reaction mixtures were carefully analyzed by GC−MS and NMR to indicate high conversions and the lack of side products.

Product Isolation and Purification. A simple and efficient procedure was developed to isolate the nitrile products pure while avoiding noticeable losses. Filtration of the reaction mixture and evaporation of the solid-free filtrate produced the crude nitrile that still contained minute quantities of inorganic materials (mostly NaBr) and ca. 0.5−2% dba. It was found that efficient purification can be achieved by redissolving the crude product in CH_2Cl_2, quickly filtering the solution through a short Celite/SiO_2 plug, and stirring the filtrate with activated charcoal for 1−2 h. This removed not only the residual inorganics, but also the dba. After the charcoal was filtered off, evaporation of the filtrate produced spectroscopically and analytically pure nitriles. The purity of the products in bulk was confirmed by satisfactory analytical data.

Scope and Limitations. As can be seen from the data in Table 2, the cyanation reaction has a broad scope. The reaction exhibits high functional group tolerance and readily occurs for both electron-deficient and electron-enriched substrates. Like any other catalytic process, however, the method is not limitation-free. The cyanide anion represents an intrinsic problem for aromatic aldehydes which readily undergo CN^--catalyzed benzoin condensation.[37] As expected (see above), Pd-catalyzed cyanation with an ionic alkali metal cyanide could not be used for substrates bearing acidic groups, for example, OH and COOH, which on contact with the cyanide salt would release HCN that instantly deactivates the catalyst. While 3-bromothiophene was cyanated quantitatively (Table 2, entry 17), 2-bromothiophene gave only 10% conversion under the same conditions, and 2- and 3-bromopyridines did not react, likely because of pyridine N-binding to active sites on Pd. Although excellent yields were obtained in the cyanation of 2-bromotoluene (entry 5) and even 2-bromoaniline (entry 11), 2-bromoanisole and 2-bromoacetophenone did not react.

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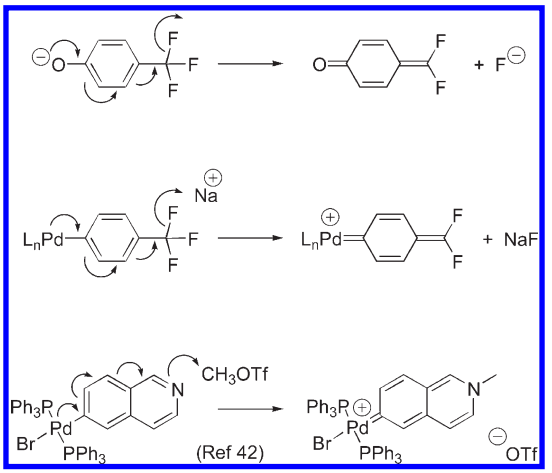
Scheme 2



Considering the smooth cyanation observed for the corresponding 3- and 4-substituted substrates (entries 6, 7, 9, and 10), it is likely that cyclopalladation[38] interferes when the ortho-isomers are used.

Surprisingly, while 3-bromobenzotrifluoride underwent smooth and clean cyanation at full conversion with ca. 100% selectivity (Table 2, entry 18), lower conversions were consistently observed for the 4- and 2-isomers (entries 19 and 20). This unexpected observation parallels the recently reported[39] strongly diminished stability of $[(t\text{-Bu}_3\text{P})\text{Pd}(\text{Br})(\text{C}_6\text{H}_4\text{CF}_3\text{-}4)]$ as compared to $[(t\text{-Bu}_3\text{P})\text{Pd}(\text{X})(\text{Ar})]$ bearing no CF_3 substituent on the σ-aryl ligand.[40] Indeed, while $[(t\text{-Bu}_3\text{P})\text{Pd}(\text{Br})(\text{Ph})]$ is stable for at least 2.5 h at 70 °C during the synthesis,[40] $[(t\text{-Bu}_3\text{P})\text{Pd}(\text{Br})(\text{C}_6\text{H}_4\text{CF}_3\text{-}4)]$ quickly decomposes after 15 min under the same conditions.[39] This accords with the lower conversion of $4\text{-CF}_3\text{C}_6\text{H}_4\text{Br}$ in the cyanation conducted at the same temperature (70 °C), where poorly stable $[(t\text{-Bu}_3\text{P})\text{Pd}(\text{Br})(\text{C}_6\text{H}_4\text{CF}_3\text{-}4)]$ is fully expected to be a key species involved in the catalytic loop as the product of oxidative addition of 4-bromobenzotrifluoride to the $t\text{-Bu}_3\text{P}$-stabilized Pd(0) (Scheme 1, Step 1). The reasons for the facile decomposition of $[(t\text{-Bu}_3\text{P})\text{Pd}(\text{Br})(\text{C}_6\text{H}_4\text{CF}_3\text{-}4)]$ have not been reported.[39] We propose that the long-known[41] negative hyperconjugation effect of the CF_3 group might be involved, as shown in Scheme 2. Fluoride elimination from $[(t\text{-Bu}_3\text{P})\text{Pd}(\text{Br})(\text{C}_6\text{H}_4\text{CF}_3\text{-}4)]$ would be facilitated by the sodium ions of NaCN, acting as a Lewis acid toward the F^-. This bears remarkable resemblance to the recently reported[42] formation of a "remote" N-heterocyclic carbene complex upon N-methylation of the σ-isoquinolinyl ligand on Pd, as shown at the bottom of Scheme 2. 4-Difluoromethylene-2,5-cyclohexadienylidene Pd derivatives are likely to be unstable and highly reactive toward nucleophiles. The negative hyperconjugation-prompted fluoride elimination (Scheme 2) provides a rationale for the low conversions of 4- and 2-bromobenzotrifluoride, in contrast with the smooth cyanation of the 3-isomer (Table 2). A separate mechanistic study to probe this hypothesis is currently underway in our laboratories.

Much less reactive than aryl bromides, chloroarenes[21e,43] were poorly efficient under the developed cyanation conditions. At 70 °C, chlorobenzene remained unreactive, and even at 110 °C (Ace pressure tube), the conversion to benzonitrile never exceeded 10% after 19−22 h in the presence or in the absence of an extra equiv of $t\text{-Bu}_3\text{P}$ per Pd (1 mol %).

CONCLUSIONS

The previously obtained[7,18] mechanistic information on Pd catalyst deactivation pathways in aromatic cyanation has been successfully used to design the first efficient and general Pd-catalyzed aromatic cyanation reaction employing NaCN, the most preferred cyanide source, in recyclable, low-boiling solvents with minimal quantities of inexpensive, nontoxic promoters. The method exhibits excellent functional group tolerance and affords aromatic nitriles from the corresponding aryl bromides at full conversion and >99% selectivity with only 0.5−1.0 mol % Pd and 6% excess NaCN within 2 h at 70 °C. To complement the process, a simple and efficient procedure has been developed to isolate the nitrile products in 88−99% yield as spectroscopically and analytically pure compounds.

EXPERIMENTAL SECTION

All chemicals were purchased from Aldrich, Alfa Aesar, and TCI chemical companies. Sodium cyanide (Aldrich; Lot: 67296PJ020) was thoroughly ground to a fine powder with a Fagor ML-300 electric coffee grinder under argon. Acetonitrile and THF were dried by distillation from P_2O_5 and sodium-benzophenone, respectively. Acetone was quickly distilled from a small amount of P_2O_5, collecting the first low-boiling fraction. All solvents were stored under argon over freshly calcined 4 Å molecular sieves. Liquid haloarenes were deoxygenated by bubbling argon through them and stored under argon over 4 Å molecular sieves prior to use. All cyanation reactions were set up and run under rigorously oxygen- and moisture-free conditions. NMR spectra were recorded on a Bruker Avance Ultrashield 400 MHz spectrometer. An Agilent Technologies 7890A chromatograph equipped with a 5975C MSD unit was used for GC−MS analysis. Elemental analyses were performed by the Microanalysis Center at the Complutense University of Madrid.

Catalyst. A dba Pd(0) complex was prepared by the Ishii method[29] from $PdCl_2$, dba, and NaOAc in MeOH. The dark purple-red microcrystalline solid that precipitated directly from the reaction mixture was used without recrystallization. A mixture of this Pd(0) dba compound that analyzed as $Pd_2(dba)_5$ (see above; 73 mg; 0.11 g-atom Pd), $t\text{-Bu}_3\text{P}$ (23 mg; 0.11 mmol), acetone (0.06 mL), and THF (4 mL) was stirred under argon overnight. The resultant catalyst solution was used for the cyanation reactions as described below.

General Procedure for Cyanation of Bromoarenes. A 20-mL screw-cap vial equipped with a magnetic stir bar was charged, in a glovebox, with a bromoarene (4.0 mmol), acetonitrile (4 mL), finely ground NaCN (0.208 g; 4.24 mmol), and either Zn dust (10 mg; 0.15 mmol) or CaH_2 powder (10 mg; 0.24 mmol). A calculated volume of the catalyst solution (see Table 2 for specifics) was added. The vial was sealed, brought out, and the mixture was vigorously stirred at 70 °C (oil bath) for 2 h. After the reaction mixture was cooled to room temperature, the product was isolated and purified in air, using one of the two procedures.

Isolation/Purification Procedure A. The reaction mixture was diluted with dichloromethane (10 mL), stirred for 10−15 min, filtered through Celite, and evaporated. After the residue was stirred with 6−7 mL of dichloromethane and 0.15 g of activated charcoal for 1.5 h, the mixture was filtered through a short silica gel plug. Evaporation of the filtrate produced the nitrile product in analytically and spectroscopically pure form (see below).

Isolation/Purification Procedure B. The reaction mixture was evaporated. The residue was treated with dichloromethane (5 mL) and the resultant suspension was filtered through a short Celite−silica gel plug. The plug was then washed with dichloromethane (2 × 1 mL). The combined dichloromethane filtrate and washings were stirred with 0.15 g of activated charcoal for 1.5 h and filtered through a short silica

gel layer. Evaporation of the filtrate produced the nitrile product in analytically and spectroscopically pure form (see below).

Benzonitrile. At full conversion, the yield was >99% (GC−MS with calibration).

2-Cyanonaphthalene was obtained and isolated in 99% yield (0.605 g) from 2-bromonaphthaline (0.828 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 7.55−7.7 (m, 3H, 3,6,7-H), 7.85−7.95 (m, 3H, 4,5,8-H), 8.2−8.3 (m, 1H, 1-H). Calcd for $C_{11}H_7N$: C, 86.3; H, 4.6; N, 9.1. Found: C, 86.3; H, 4.8; N, 8.9.

4-Methylbenzonitrile was obtained and isolated in 93% yield (0.436 g) from 4-bromotoluene (0.492 mL; 0.684 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 2.4 (s, 3H, CH_3), 7.2−7.3 (m, 2H, 3,5-H), 7.45−7.6 (m, 2H, 2,6-H). Calcd for C_8H_7N: C, 82.0; H, 6.0; N, 12.0. Found: C, 81.8; H, 6.1; N, 11.5.

3-Methylbenzonitrile was obtained and isolated in 97% yield (0.453 g) from 3-bromotoluene (0.485 mL; 0.684 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 2.4 (s, 3H, Me), 7.3−7.5 (m, 4H, 2,4,5,6-H). Calcd for C_8H_7N: C, 82.0; H, 6.0; N, 12.0. Found: C, 82.1; H, 6.2; N, 11.5.

2-Methylbenzonitrile was obtained and isolated in 94% yield (0.438 g) from 2-bromotoluene (0.482 mL; 0.684 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 2.5 (s, 3H, Me), 7.2−7.35 (m, 2H, 3,5-H), 7.4−7.5 (m, 1H, 6-H), 7.5−7.6 (m, 1H, 4-H). Calcd for C_8H_7N: C, 82.0; H, 6.0; N, 12.0. Found: C, 81.5; H, 6.2; N, 11.6.

3-Acetylbenzonitrile was obtained and isolated in 99% yield (0.575 g) from 3-bromoacetophenone (0.534 mL; 0.796 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 2.6 (s, 3H, Me), 7.55−7.65 (m, 1H, 5-H), 7.8−7.9 (m, 1H, 6-H), 8.1−8.2 (m, 1H, 4-H), 8.2−8.25 (m, 1H, 2-H). Calcd for C_9H_7NO: C, 74.5; H, 4.9; N, 9.7. Found: C, 74.6; H, 5.0; N, 9.4.

4-Acetylbenzonitrile was obtained and isolated in 99% yield (0.575 g) from 4-bromoacetophenone (0.796 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 2.6 (s, 3H, Me), 7.7−7.8 (m, 2H, 2,6-H), 8.0−8.1 (m, 2H, 3,5-H). Calcd for C_9H_7NO: C, 74.5; H, 4.9; N, 9.7. Found: C, 74.7; H, 4.9; N, 9.6.

4-Nitrobenzonitrile was obtained and isolated in 99% yield (0.586 g) from of 4-bromonitrobenzene (0.808 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 7.8−7.95 (m, 2H, 2,6-H), 8.3−8.4 (m, 2H, 3,5-H). Calcd for $C_7H_4N_2O_2$: C, 56.8; H, 2.7; N, 18.9. Found: C, 57.2; H, 2.8; N, 18.6.

4-Methoxybenzonitrile was obtained and isolated in 99% yield (0.530 g) from 4-bromoanisole (0.502 mL; 0.748 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 3.85 (s, 3H, Me), 6.9−7.0 (m, 2H, 3,5-H), 7.5−7.6 (m, 2H, 2,6-H). Calcd for C_8H_7NO: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.6; H, 5.4; N, 10.2.

3-Methoxybenzonitrile was obtained and isolated in 99% yield (0.528 g) from 3-bromoanisole (0.509 mL; 0.748 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 3.8 (s, 3H, Me), 7.1−7.15 (m, 2H) and 7.2−7.25 (m, 1H, 2,4,6-H), 7.3−7.4 (m, 1H, 5-H). Calcd for C_8H_7NO: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.5; H, 5.5; N, 10.3.

2-Aminobenzonitrile was obtained and isolated in 99% yield (0.470 g) from 2-bromoaniline (0.688 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 4.0−4.7 (br s, 2H, NH_2), 6.65−6.8 (m, 2H, 3,5-H), 7.3−7.35 (m, 1H, 4-H), 7.35−7.45 (m, 1H, 6-H). Calcd for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.4; H, 5.3; N, 22.2 (N content outside the range of the method).

4-Aminobenzonitrile was obtained and isolated in 99% yield (0.470 g) from 4-bromoaniline (0.688 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 3.9−4.4 (br s, 2H, NH_2), 6.55−6.7 (m, 2H, 3,5-H), 7.35−7.45 (m, 2H, 2,6-H). Calcd for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.5; H, 5.2; N, 23.1. (N content outside the range of the method).

4-(Dimethylamino)benzonitrile was obtained and isolated in 99% yield (0.582 g) from 4-bromo-*N*,*N*-dimethylaniline (0.800 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 3.05 (s, 6H, NCH_3), 6.6−6.7 (m, 2H, 3,5-H), 7.4−7.5 (m, 2H, 2,6-H). Calcd for $C_9H_{10}N_2$: C, 73.9; H, 6.9; N, 19.2. Found: C, 74.2; H, 6.7, N, 18.9.

Ethyl 4-cyanobenzoate was obtained and isolated in 99% yield (0.696 g) from ethyl 4-bromobenzoate (0.640 mL; 0.916 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 1.4 (t, ^3J = 7.1 Hz, 3H, CH_3), 4.4 (q, ^3J = 7.1 Hz, 2H, CH_2), 7.7−7.8 (m, 2H, 3,5-H), 8.1−8.2 (m, 2H, 2,6-H). Calcd for $C_{10}H_9NO_2$: C, 68.6; H, 5.2; N, 8.0. Found: C, 68.8; H, 5.2; N, 7.9.

4-Chlorobenzonitrile was obtained and isolated in 95% yield (0.523 g) from 4-bromochlorobenzene (0.766 g). The product contained ca. 4 mol % of terephthalonitrile (NMR, GC−MS). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 7.45−7.5 (m, 2H, 2,6-H), 7.55−7.65 (m, 2H, 3,5-H).

4-Fluorobenzonitrile was obtained and isolated in 97% yield (0.468 g) from 4-bromofluorobenzene (0.439 mL; 0.700 g). To avoid significant losses of this more volatile product, the reaction solvents were carefully removed on a rotary evaporator at 500 mbar/80 °C. For the same reason, care was exercised evaporating dichloromethane in the final isolation step. The isolated product contained ca. 4 mol % of CH_2Cl_2 (NMR, GC−MS). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 7.1−7.25 (m, 2H, 3,5-H), 7.65−7.75 (m, 2H, 2,6-H).

3-Cyanothiophene was obtained and isolated in 93% yield (0.568 g) from 3-bromothiophene (0.525 mL; 0.913 g; 5.6 mmol) and NaCN (0.291 g; 5.9 mmol) in 5.6 mL of acetonitrile with 1% of the catalyst. ^{1}H NMR ($CDCl_3$, 25 °C), δ: 7.3 (dd, $^3J_{4,5}$ = 5.1 Hz, $^4J_{4,2}$ = 1.2 Hz, 1H, 4-H), 7.4 (dd, $^3J_{5,4}$ = 5.1 Hz, $^4J_{5,2}$ = 2.9 Hz, 1H, 5-H), 7.95 (dd, $^4J_{2,4}$ = 1.2 Hz, $^4J_{2,5}$ = 2.9 Hz, 1H, 2-H). The spectroscopically pure product was additionally purified on a short silica gel column prior to elemental analysis. Calcd for C_5H_3NS: C, 55.0; H, 2.8; N, 12.8; S, 29.4. Found: C, 55.4; H, 3.1; N, 12.7; S, 29.1.

3-Trifluoromethylbenzonitrile was obtained and isolated in 88% yield (0.602 g) from 3-bromobenzotrifluoride (0.559 mL; 0.900 g). ^{1}H NMR ($CDCl_3$, 25 °C), δ: 7.6−7.7 (m, 1H, 5-H), 7.8−7.9 (m, 2H, 4,6-H), 7.9−7.95 (m, 1H, 2-H). Calcd for $C_8H_4F_3N$: C, 56.2; H, 2.4; N, 8.2. Found: C, 56.6; H, 2.8; N, 8.0.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR spectra of the isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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